The DAS Is the Most Specific Measure, But a Patient Questionnaire Is the Most Informative Measure to Assess Rheumatoid Arthritis

Quantitative assessment of patients with rheumatic diseases differs from quantitation of patient status in many other chronic diseases such as hypertension or hypercholesterolemia by the absence of a single measure to serve as a "gold standard" for clinical trials, clinical research, and standard clinical care. Therefore, "pooled indices"[1] of several measures have been developed to assess patient status for many rheumatic diseases including rheumatoid arthritis (RA)[2,3], systemic lupus erythematosus[4], ankylosing spondylitis[5], psoriatic arthritis[6], and vasculitis[7]. A pooled index provides statistical power to detect change from baseline to subsequent visits in clinical trials when individual measures are inadequate[1].

The major pooled indices to assess RA are the American College of Rheumatology (ACR) Core Data Set[2] and the Disease Activity Score (DAS)[3]. These standardized indices have advanced a common standardized metric for clinical trials and clinical research. The DAS presents an important advantage over ACR criteria in providing an absolute number, rather than a "change score" from one time point to another. Thus, a DAS value can be described for a given patient on a given day in any clinical setting, to be compared to other patients, to past and future scores in the same patient, and/or for analyses in groups for comparison with other groups of patients.

Three of the 4 measures included in the DAS, swollen joint count, tender joint count, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), are reversible measures of inflammation, in contrast to cumulative, irreversible measures of damage, such as radiographic joint destruction. The fourth measure, patient estimate of global status, is sensitive to both activity and damage. Measures of inflammatory activity in RA are required to document efficacy of any therapy in a clinical trial. However, measures of activity are surrogate measures for longterm severe outcomes, such as functional disability, work disability, joint replacement surgery, premature mortality, and costs. Persistent inflammatory activity leads to development of longterm damage, and clinical trial data are interpreted based on this prognostic association. However, the surrogate measures are far from perfect measures as prognostic of longterm damage.

These considerations indicate that the DAS may be the most specific measure of inflammation for clinical trials, clinical research, and clinical care. A patient who is improved in swollen or tender joints clearly has improvement in their underlying disease. However, the DAS is a relatively poor measure of the overall status of patients with RA.

As a measure of clinical status in patients with RA the DAS is subject to 3 important limitations:

1. Measures of inflammation such as swollen joint count, tender joint count, as well as ESR, have historically been likely to be stable or improve over a 5 year period, while patients continue to experience longterm damage as assessed by joint deformity, radiographic progression, and functional disability according to Health Assessment Questionnaire (HAQ) scores[8-16]. One example from the author's clinical research[17] indicated that swollen joint counts, tender joint counts, and ESR were somewhat improved in a cohort of 100 patients between 1985 and 1990, while HAQ scores remained stable, and joint deformity, radiographic scores, grip strength, and walking time indicated progression of joint damage (Figure 1). Indeed, there is virtually no published report in which there was not improvement in patients who continued to be monitored in rheumatology clinical settings according to swollen joint count, tender joint count, or acute phase reactant over 5–15 years, although progression of radiographic changes or functional disability occurred simultaneously.

Therefore, the DAS may indicate a short term response to therapy, but will not necessarily indicate a longterm response with improved outcomes. Patients with long duration of RA may have few swollen or tender joints, but many deformed joints, particularly if methotrexate and/or anti-tumor necrosis factor-α were introduced many years after the onset of damage, according to a traditional "pyramid" strategy[18,19]. However, these patients do not represent desirable outcomes for people with RA.

2. The measures included in the DAS are not the most effective predictors of longterm outcomes in RA. DAS values are invariably less informative than patient questionnaire scores according to the HAQ or HAQ derivative, to

predict future functional status[9,20], work disability[21-23], costs[24], joint replacement surgery[25], and premature death[9,17,26-31]. In the cohort analyzed between 1985 and 1990 noted above, the prospective prognosis of mortality over 5 years was much greater according to a modified HAQ (MHAQ) than according to swollen joint count, tender joint count, or laboratory tests[17]. In regression analysis, the most effective predictors of 5 year mortality were age, comorbidities, and functional disability according to a MHAQ[17].

Further, in another study of these patients, the most effective clinical measure to distinguish patients who were receiving work disability payments versus working full time was the MHAQ[21]. Other clinical measures including radiographic scores, joint count scores, and laboratory data indicated poorer status in patients who were disabled versus patients who were working fulltime. However, these traditional measures did not contribute further to identification of work or disability status (or premature mortality) than MHAQ scores[17,21], which was largely determined by demographic variables, including age, occupation, as well as duration of disease[17,21]. It may be argued that the HAQ scores reflect rather than predict poor status and poor outcomes, but nonetheless if one wishes to predict what is likely to happen in a patient over the next 5 to 15 years, the HAQ or HAQ derivative is a more effective predictor than any components of the DAS. Even joint replacement surgery, which in a sense depends on an abnormal radiograph, is better predicted by HAQ score than by joint examination or radiograph[25]. These findings reflect that decisions for joint replacement in actual clinical care are based primarily on patients' desire for the procedure beyond "objective" criteria.

3. There is rather poor agreement between DAS scores and rheumatologists' global assessment of patient status[32]. Although these measures are correlated, as anticipated, many discrepancies are seen in either direction. These findings suggest that the DAS may not necessarily reflect what rheumatologists (at least in the United States) believe to be the patient status at the time. An absolute DAS score of less than 2.6 indicates low disease activity. The patient certainly has better status than if these values are higher. However, if only DAS is collected in standard clinical care, without the HAQ or HAQ derivative, clinicians cannot document further improved longterm outcomes in RA at this time.

Despite being the most specific measure of inflammation, the DAS is subject to additional limitations:

1. The relative efficiencies of components of the DAS in clinical trials are no greater, and are often lesser, than those of patient reported outcomes. In a clinical trial involving methotrexate, leflunomide, and placebo, for example, the tender and swollen joint counts had lower relative efficiency to detect differences between active versus control treatment than did the HAQ, MHAQ, or patient assessment of global status[33]. The reason may be that swollen joints are much less likely to improve in joints that are damaged; therefore, particularly in clinical trials involving patients with long-standing disease, the swollen joint count is not an efficient measure[33].

2. The reproducibility of swollen and tender joint counts is limited[34]. Indeed, patient questionnaire responses turn out to be more reproducible than observer derived information, provided they are obtained through a self-report questionnaire[35]. There may be several reasons for this.

First, self-report involves a single observer, the patient, while a joint count involves 2 observers, the patient and the assessor. Interpretation of pressure to assess tenderness and swelling may vary from one assessor to another and from one patient to another, even for the same assessor or patient from one day to another. Of course, the patient as an individual may also vary from one day to another, but less variation is seen in measures involving a single observer. Certain information, such as diagnosis, requires an observer for accuracy[36], but obtaining a pain score or responses to "Can you dress yourself?" does not.

Second, there is an unconscious (not deliberate) observer bias, when screening a person for a clinical trial, to rate equivocal joints as more likely swollen or tender. After a year of monthly visits, regardless of being randomized to active or control treatment, the bias is that the joint is not swollen or tender. The likelihood of this phenomenon occurring is seen in examining data in the leflunomide, methotrexate, and placebo study, in which levels of improvement in joint count are greater than those of questionnaire scores or laboratory data[33].

The best 2 measures to document improvement of the longterm course of RA are a radiograph and a patient questionnaire, which assess cumulative damage. The absence of radiographic progression or functional disability would indicate slowing or progression of longterm damage. Both radiographic and functional disability status can be assessed according to quantitative scales, such as Sharp[37], Larsen[38], van der Heijde[39] scores, or HAQ[35] or multidimensional HAQ (MDHAQ)[40]. However, it is difficult to quantitate radiographs in standard rheumatology care; even clinical trials generally include at least 2 readers and often have pretrial workshops to standardize the measure methodology. By contrast, a score on the HAQ or HAQ derivative is easily assessed in standard clinical care, as the patient does most of the work. Scores are easily quantitated by the clinician, particularly on a MDHAQ, which includes scoring templates[41]. (The practice in some sites in which a nurse or other health professional assists the patient to complete a questionnaire is undesirable because it adds a second observer.)

Therefore the most informative measure to monitor the longterm course of rheumatic diseases is a patient question-

naire. Further, as patient questionnaires are sensitive to short term changes in status, albeit with less specificity than the DAS, the HAQ or HAQ derivative would appear the most informative measure of status in RA. The simplest methodology is to provide a questionnaire to every patient when they register for every visit. Even a patient seen twice within a month should be asked to repeat the questionnaire with the explanation that "if there is a reason to be seen again, there is a reason to be assessed." Routine administration of a patient questionnaire could greatly improve the scientific basis of clinical rheumatology.

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